• Clinical Research •

# Comparison of inebilizumab or rituximab in addition to glucocorticoid therapy for neuromyelitis optica spectrum disorders

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## Abstract

● **AIM:** To investigate the short-term efficacy and safety of inebilizumab for neuromyelitis optica spectrum disorders (NMOSD).

● **METHODS:** A total of 33 patients with NMOSD treated with inebilizumab (Group INB, *n*=15) or rituximab (Group RTX, *n*=18) in addition to high-dose glucocorticoids were included. Both groups underwent hormone shock therapy during the acute phase. Subsequently, Group INB received inebilizumab injections during the remission phase, while Group RTX received rituximab injections. A comparison of aquaporins 4 (AQP4) titer values, peripheral blood B lymphocyte counts, and visual function recovery was conducted before and 8wk after treatment. Additionally, adverse reactions and patient tolerability were analyzed after using inebilizumab treatment regimes.

● **RESULTS:** Following inebilizumab treatment, there was a significantly improvement in the visual acuity of NMOSD patients ($P$<0.05), accompanied by a notable decrease in AQP4 titer values and B lymphocyte ratio ($P$<0.05). Moreover, inebilizumab treatment showed a partial effect in preventing optic nerve atrophy ($P$<0.05). However, there were no significant differences in other therapeutic effects compared to rituximab, which has previously demonstrated substantial therapeutic efficacy ($P$>0.05). Furthermore, inebilizumab exhibited higher safety levels than that of rituximab injections.

● **CONCLUSION:** The combination of inebilizumab and high-dose glucocorticoids proves to be effective. In comparison to rituximab injections, inebilizumab displays better tolerance and safety. Moreover, it demonstrates a partial effect in preventing optic nerve atrophy. Thus, it stands as an effective method to reduce the disability rates and improve the daily living ability of patients with NMOSD.

● **KEYWORDS:** neuromyelitis optica spectrum disorders; inebilizumab; rituximab; glucocorticoids

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## INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) is a recurrent and incapacitating autoimmune disease affecting the central nervous system, primarily targeting the optic nerve and spinal cord[1]. The disorders show a relatively high prevalence in the Asian population. In China, epidemiological data reveals an annual average incidence rate of NMOSD at 0.278/100 000, with adults experiencing an annual incidence rate of 0.374/100 000 and children at 0.075/100 000. Geographically, NMOSD incidence demonstrates no significant difference in distribution, but the prevalence among women is notably higher than in men, with a ratio of 9:1. The onset of NMOSD primarily occurs within two age peaks, between 20-40 years old and 50-60 years old[2-3]. Clinical manifestations encompass visual loss, paralysis, neuralgia, respiratory failure, *etc*. Notably, the recurrence rate for NMOSD is exceedingly high, reaching 97% within 5y, often resulting in cumulative residual effects. Every recurrence may lead to vision loss, impaired mobility, and in severe cases, life threatening complications. Hence, the paramount goal in managing this condition is to identify effective therapeutic agents that alleviate acute symptoms and reduce relapses during remission.

Studies have shown that inebilizumab injection, a humanized monoclonal antibody targeting CD19 on the surface of B cells, exerts its effects by binding to CD19 on B cells, plasma cells, and plasma blast, causing their destruction and subsequently

reducing the generation and release of pathogenic aquaporins 4 antibodies (AQP4 IgG). This mechanism helps control disease recurrence[4]. This study employed inebilizumab injection to treat NMOSD, evaluating treatment efficacy, tolerability, and short-term recurrence, thereby contributing valuable insights for the clinical management of NMOSD.

## SUBJECTS AND METHODS

**Ethical Approval** This study was conducted following the patients' and their family members' informed consent to receive immunosuppressive therapy. Science and Technology Ethics (review) Committee of Xi'an People's Hospital (Xi'an Fourth Hospital) approved the study.

**General Information** We selected 33 patients diagnosed with NMOSD admitted to our hospital between April and October 2023. Inclusion criteria were as follows: 1) All patients met the 2015 NMOSD international diagnostic consensus[5]; 2) received methylprednisolone sodium succinate injection and subsequent treatment with either inebilizumab injection or Rituximab injection; 3) Underwent serum AQP4 antibody testing; 4) Able to undergo long-term follow-up. Exclusion criteria included: 1) Patients with severe infections, tumors, or other immune diseases; 2) Patients using traditional Chinese medicine to recurrence prevention; 3) Patients using low-doses corticosteroids alone for seizure prevention. According to the treatment plan, patients were divided into inebilizumab Group (Group INB, $n$=15) and rituximab Group (Group RTX, $n$=18, of which three patients withdrew due to severe adverse reactions).

**Methods** During the acute phase, both patient groups received high-dose glucocorticoids therapy (intravenous drip + oral regimen). Initially, intravenous methylprednisolone sodium succinate injection (Chongqing Huabang Pharmaceutical Co., Ltd., China. National Pharmaceutical Approval No. H20143135) was administered using a dose-decreasing regimen. The regimen commenced with an initial dose of 500 mg/d for 3 consecutive days. Subsequently, starting from the 4$^{th}$ day, the dosage was adjusted to 250 mg/d for 3d. From the 7$^{th}$ day onwards, the dosage was further decreased to 125 mg/d for another 3d. This was followed by an oral regimen using prednisone acetate tablets (Zhejiang Xianju Pharmaceutical Co., Ltd., China; National Drug Approval Number H33021207). A gradual dose reduction was employed, starting at 1 mg/kg•d, reducing by 5-10 mg per week, and maintaining a dosage of 5 mg/d for at least 2wk. To mitigate potential adverse reactions caused by hormone therapy, omeprazole enteric coated capsules (Shandong Luoxin Pharmaceutical Co., Ltd., China; National Drug Approval Number H2033444), calcium carbonate D3 tablets (Huishi Pharmaceutical Co., Ltd., China; National Drug Approval Number H10950029), and potassium chloride tablets (Shenzhen Zhonglian Pharmaceutical Co., China; National Drug Approval Number H20033371) were administered. Before initiating immunosuppressive agents' infusion, pre-medication was administered to prevent allergies and infusion reactions. This pre-medication included a 1 mL intramuscular injection of diphenhydramine hydrochloride injection (Suicheng Pharmaceutical Co., Ltd., China; National Drug Approval Number H41021264) and one oral sustained-release capsule of ibuprofen (North China Pharmaceutical Co., Ltd., China; National Drug Approval Number H20193365). Subsequently, in addition to the aforementioned treatment, Group RTX received rituximab injection (Roche Pharma, Schweiz, AG, Imported Drug Registration Certificate S20170002) at a dosage of 100 mg intravenous drip once every 2wk for a total of 4 treatments. In contrast, Group INB received AstraZeneca Nijmegen B.V. (Imported Drug Registration Certificate Number: JS20220006) at a dosage of 300 mg intravenous drip once every 2wk for a total of 2 treatments.

**Observation Indicators** 1) Vision assessments were conducted using the "Standardized logMAR Logarithmic Vision Chart"; 2) Recovery of optic nerve atrophy; 3) Recovery of visual evoked potential (VEP)-P100 peak time and amplitude; 4) Proportion of B lymphocyte subpopulations and IgG titer value of anti-AQP4 antibody [detection method: indirect immunofluorescence (IIFT), tissue based assay (TBA)+cell based transfection immunofluorescence assay (CBA)]; 5) Compare the occurrence of adverse reactions during treatment between the two groups.

**Statistical Analysis** Data analysis was performed using SPSS19.0 Software package. Measurement data were presented as mean±standard deviation. Paired $t$-tests were utilized to and compare pre- and post-treatment measurements within each group, while independent sample $t$-tests were employed for comparisons between the two groups. Statistically significant was set at $P$<0.05 to determine differences between groups.

## RESULTS

The study group comprised one male and 14 female patients, with an average age of 46±4.7y, and an average disease duration of 0.8±0.24y; Group RTX included 2 males and 13 females, with an average age of 42±5.6y and an average disease of 0.7±0.33y.

**Comparison of Visual Acuity and Recovery of Optic Disc Atrophy Before and After Treatment Between Two Groups**

The independent sample $t$-test results revealed no significant difference between the Group INB and Group RTX ($P$>0.05). However, the paired sample $t$-test demonstrated a notable difference in visual acuity before and after treatment between Group INB and Group RTX ($P$<0.05). Similarly, there was a significant difference in peripheral disc nerve fiber thickness (nasal and temporal) before and after treatment between Group

**Table 1 Changes in visual acuity before and after treatment with inebilizumab and rituximab** mean±SD, logMAR

| Project | Visual acuity (logMAR) | | | |
|---|---|---|---|---|
| | Before treatment | After treatment | *t* | *P* |
| Inebilizumab (*n*=15) | 1.41±1.03 | 0.62±0.59 | 3.691 | 0.002 |
| Rituximab (*n*=15) | 0.91±0.58 | 0.59±0.57 | 3.166 | 0.007 |
| *t* | 1.636 | 0.126 | | |
| *P* | 0.116 | 0.900 | | |

**Table 2 Changes in peripheral disc nerve fiber thickness before and after treatment with inebilizumab and rituximab** mean±SD, μm

| Project | Peripheral disc nerve fiber thickness (upper and lower) | | | | Peripheral disc nerve fiber thickness (nasal and temporal) | | | |
|---|---|---|---|---|---|---|---|---|
| | Before treatment | After treatment | *t* | *P* | Before treatment | After treatment | *t* | *P* |
| Inebilizumab (*n*=15) | 114.37±31.99 | 101.37±30.21 | 1.633 | 0.125 | 70.5±23.61 | 57.2±21.18 | 2.331 | 0.035 |
| Rituximab (*n*=15) | 127.23±49.43 | 101.43±32.66 | 3.596 | 0.003 | 73.7±22.79 | 57.77±18.25 | 5.117 | 0.000 |
| *t* | -0.846 | -0.006 | | | -0.378 | -0.079 | | |
| *P* | 0.405 | 0.995 | | | 0.709 | 0.938 | | |

**Table 3 Recovery of optic nerve function before and after treatment with inebilizumab and rituximab** mean±SD

| Project | P-VEP15min (P100), ms | | | | P-VEP15min (N75-P100), μV | | | |
|---|---|---|---|---|---|---|---|---|
| | Before treatment | After treatment | *t* | *P* | Before treatment | After treatment | *t* | *P* |
| Inebilizumab (*n*=15) | 120.28±13.22 | 114.41±10.36 | 1.435 | 0.173 | 7.11±4.78 | 7.63±5.05 | -1.283 | 0.220 |
| Rituximab (*n*=15) | 119.35±13.21 | 117.97±9.64 | 0.429 | 0.674 | 7.71±4.28 | 7.51±4.19 | 0.417 | 0.683 |
| *t* | 0.193 | -0.974 | | | -0.362 | 0.071 | | |
| *P* | 0.848 | 0.338 | | | 0.720 | 0.944 | | |

VEP: Visual evoked potential.

**Table 4 Changes in the IgG titer value of anti-AQP4 antibody and B lymphocyte ratio before and after treatment with inebilizumab and rituximab** mean±SD

| Project | The IgG titer value of anti AQP4 antibody | | | | B lymphocyte ratio | | | |
|---|---|---|---|---|---|---|---|---|
| | Before treatment | After treatment | *t* | *P* | Before treatment | After treatment | *t* | *P* |
| Inebilizumab (*n*=15) | 219.2±331.49 | 11.87±13.32 | 2.504 | 0.025 | 12.22±5.85 | 0.06±0.08 | 8.062 | 0.000 |
| Rituximab (*n*=15) | 79.6±102.55 | 9.6±10.23 | 2.801 | 0.014 | 10.35±5.27 | 0.11±0.13 | 7.593 | 0.000 |
| *t* | 1.558 | 0.523 | | | 0.921 | -1.302 | | |
| *P* | 0.138 | 0.605 | | | 0.365 | 0.204 | | |

Ig: Immune globulin; AQP4: Aquaporins 4.

INB and Group RTX ($P$<0.05). Conversely, no significant difference was observed in peripheral disc nerve fiber thickness (upper and lower) before and after treatment between Group INB and Group RTX ($P$<0.05). The finding indicate that both Group INB and Group RTX exhibited positive effects in promoting visual recovery. Notably, Group INB demonstrated a capacity to prevent partial atrophy of nerve fiber thickness around the optic disc, while Group RTX did not exhibit similar preventive effects (Tables 1 and 2).

**Visual Function Recovery Before and After Treatment in the Two Groups** The independent sample *t*-test results indicated no significant difference between the Group INB and Group RTX ($P$>0.05). Additionally, the paired sample *t*-test results demonstrated no significant differences ($P$>0.05) in the peak time and amplitude of VEP-P100 before and after treatment in both groups. These findings suggest that both Group INB and Group RTX exhibited limited therapeutic effects in promoting visual function recovery (Table 3).

**Changes in IgG Titer Value of Anti-AQP4 Antibody and B Lymphocyte Ratio Before Treatment Between the Two Groups** The independent sample *t*-test results revealed no significant difference between the Group INB and Group RTX ($P$>0.05). However, the paired sample *t*-test results displayed a significant reduction in both AQP4 titer and B lymphocyte ratio before and after treatment in both group, demonstrating significant differences ($P$<0.05). These findings indicate that both the experimental and Group RTX achieved substantial therapeutic effects in controlling disease progression and preventing recurrence (Table 4).

**Comparison of Adverse Reactions Between Two Groups** In Group INB, one patient encountered mild joint pain symptoms during infusion, with recovery within 2h post-

infusion. However, two patients in Group RTX showed significant systemic itching accompanied by rash and erythema during the infusion process. Additionally, one patient exhibited pronounced symptoms of shivering, fever, and a runny nose. All of these patients exhibited improvement in symptoms following medication discontinuation and intramuscular injection of promethazine. As a result of severe adverse reactions, these three patients withdrew from Group INB after the first medication. Furthermore, one case in Group INB developed mild joint pain symptoms which resolved 2h post-infusion. Additionally, another case experienced mild skin itching without rash or erythema, recovering within 2h after infusion.

## DISCUSSION

NMOSD is an antigen-antibody mediated inflammatory demyelinating disease of the central nervous system mediated by humoral immunity. In clinical practice, it predominantly manifests as severe optic neuritis and acute myelitis, characterized by high recurrence rate, substantial disability, and residual accumulation effects. Unpredictable recurrence in patients can lead to severe nerve damage and accumulation residual effects[6-7]. Therefore, the pillars of NMOSD therapy are attack treatment and prevention strategies to minimize neurological disability progression in NMOSD patients.

Current understanding suggests that AQP4 IgG play a significant role in NMOSD's occurrence, progression, and prognosis[8]. Although the precise cause of NMOSD remains elusive, evidence points to the pathogenicity of AQP4 antibodies targeting the predominant astrocyte water channel in the central nervous system. Plasma B cells act as the primary source of AQP4-IgG. During NMOSD relapses, alterations in peripheral blood B cell subpopulations and AQP4-IgG titers in patients can reflect the attack's severity and prognosis[9-10]. Therefore, the depletion of peripheral blood B cell subpopulations and reduction of AQP4-IgG titers are crucial steps for preventing NMOSD recurrence and improving patient prognoses.

The primary treatment for acute exacerbation of NMOSD typically is high-dose glucocorticoids therapy, intravenous immunogloblin, and plasma exchange, with high-dose glucocorticoids being the most commonly utilized approach, plasma exchange and intravenous immunogloblin can improve the vision and symptoms of patients with neuromyelitis optica (NMO)-optic neuritis patients with recurrent and glucocorticoid resistance[11]. During the remission phase, sequential treatment aims to mitigate disease recurrence, lower the risk of blindness, and reduce disability rates. This regimen comprises two facets: oral immunosuppressants and biological agents.

Immunosuppression forms a long-term requirement, given the high risk of recurrence following treatment cessation[12]. Mycophenolate mofetil (MMF) stands as one of the most commonly used oral immunosuppressants. Zeng *et al*'s[13] study find MMF treatment for AQP4 antibody positive NMOSD can reduce the annualized attack rate (ARR) of optic neuritis to a certain extent and protect the visual function of patients. Prior to the approval of monoclonal antibody therapy, unapproved methods for preventing recurrence mainly relied on medications like rituximab and azathioprine[14]. Rituximab, a human/mouse chimeric monoclonal antibody, specifically targets the CD20 antigen on the surface of B lymphocytes, triggering B lymphocyte lysis through immune responses[15-16]. Mechanisms underlying cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cytotoxicity (ADCC). The successful use of rituximab for over 15y in treating NMOSD by depleting B cells through anti-CD20 antibodies highlights its efficacy. In recent times, four preventive immunotherapies have received approval for AQP4-IgG-positive NMOSD across various regions worldwide: eculizumab, ravulizumab, inebilizumab, and satralizumab. These novel drugs may potentially substitute rituximab and traditional immunosuppressive therapies, which have been the primary treatment for both AQP4-IgG-positive and -negative NMOSD[17].

Inebilizumab is a humanized, non-glycosylated IgG1 monoclonal antibody targeting CD19 on the surface of B cells[18]. While the exact mechanism of inebilizumab in treating NMOSD remains under investigation, it is speculated that it binds to CD19, on the surface of B cells, prompting antibody dependent cell lysis. This process effectively eliminates B cells, potentially inhibiting the onset of NMOSD[19-20]. CD19 and CD20 are both surface markers specifically expressed on B cells, CD19, expressed on progenitor B cells, pre-B cells, immature B cells, mature B cells, memory B cells, plasma cells, and some plasma blast, wider than CD20 on B cells. CD20 is also present in a small subset of T cell[21]. Therefore, inebilizumab can directly target cells that produce pathogenic AQP4-IgG, while antibodies targeting CD20 are not directly targeted[22].

Animal studies suggest inebilizumab's higher affinity and persistence compared to rituximab. The antibody concentration required for B cell consumption is significantly lower than that of rituximab, and the depletion effect of B cells is significantly longer than that of rituximab[17,19]. The N-MOmentum study (NCT02200770)[23] was a multicenter, double-blind, randomized, placebo-controlled phase 2/3 study aimed at evaluating the efficacy and safety of inebilizumab in treating adult patients with NMOSD. The results showed that the use of inebilizumab was effective in preventing NMOSD recurrence: it reduced NMOSD related hospitalization rates, significantly delayed disability progression, and reduced the number of

new magnetic resonance (MRI) lesions. However, current research suggests inebilizumab might not alleviate optic nerve inflammation severity or promote optic nerve recovery[17-18,20]. Regarding the adverse events (AEs), inebilizumab's incidence rates were comparable to the placebo group. Common AEs associated with inebilizumab and occurring more frequently than placebo are urinary tract infections (11% *vs* 9%) and joint pain (10% *vs* 4%), with additional events such as headache, back pain, nasopharyngitis, and diarrhea reported at an incidence of ≥5%[20-21]. Immunosuppressive therapy may increase the risk of malignant tumors and infections, while also leading to progressive multifocal white matter disease (PML) and reactivation of hepatitis B, tuberculosis (TB), and hepatitis C viruses. However, to date, no cases of malignant tumors or PML have been reported among patients receiving inebilizumab treatment. The infection rate of patients receiving inebilizumab for ≥4y is 71.4 events per 100 person years, occurring in 79% of patients[22].

This study observed no serious adverse reactions in the study group during follow-up. However, three patients in Group RTX experienced significant allergic reactions and consequently withdrew from treatment. Notably, two of these patients opted to continue treatment with inebilizumab after switching from Group RTX and did not encounter any allergic reactions. Another patient chose to continue treatment with oral MMF tablets due to economic reasons. While inebilizumab displayed slightly superior outcomes in preventing optic nerve atrophy, the substantial leap in safety over traditional drugs remains noteworthy. This is the first head-to-head study to compare the efficacy and safety of rituximab and inebilizumab, two B-cell deplete agents, in the treatment of optic neuritis, and the efficacy of inebilizumab in the treatment of optic atrophy was surprising[24-25]. Several limitations warrant acknowledgment in this study, including an insufficient sample size and a relatively short follow-up duration of only half a year. This shorter follow-up might have affected the completeness of recurrence evaluations, potentially impact on the results. Future plans involve continuous long-term follow-up of ongoing patient treatment to comprehensively assess recurrence rates and side effects over extended periods. Furthermore, inebilizumab is relatively expensive in unit price, and its efficacy and safety still need to be validated with larger and larger sample data.

In summary, this study underscores the significant efficacy of inebilizumab in preventing NMOSD recurrence and alleviating its symptoms. It notably demonstrates a low incidence of adverse reactions and high safety compared to rituximab injection. For adults with AQP4 antibody serum positive NMOSD, inebilizumab emerges as a promising treatment option during the remission phase. However, given the mentioned study limitations, further extensive research is needed on the exact long-term efficacy and adverse reactions of inebilizumab in the treatment of NMOSD.

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